PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32911A	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/002610	International filing date *(day/month/year)* 12.03.2004	Priority date *(day/month/year)* 14.03.2003
International Patent Classification (IPC) or national classification and IPC A61K31/427, A61P35/00		
Applicant NOVARTIS AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand 14.10.2004	Date of completion of this report 04.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Paul Soto, R Telephone No. +49 89 2399-7346

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/002610

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-10 as originally filed

   Claims, Numbers

   1-11 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-7, 10 (industrial applicability)

because:

☒ the said international application, or the said claims Nos. 1-7, 10 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-11
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	11; for claims 1-10 see separate sheet
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 1-7 and 10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. Reference is made to the following documents:
   - **D1:** WO 99/02514 A (SQUIBB BRISTOL MYERS CO) 21 January 1999 (1999-01-21)
   - **D2:** WO 02/058700 A (SQUIBB BRISTOL MYERS CO) 1 August 2002 (2002-08-01)
   - **D3:** PATENT ABSTRACTS OF JAPAN vol. 2002, no. 02, 2 April 2002 (2002-04-02) & JP 2001 288097 A (PG-TXL CO LP), 16 October 2001 (2001-10-16)
   - **D4:** KIM JAE-CHUL ET AL: "Potential radiation-sensitizing effect of semisynthetic epothilone B in human lung cancer cells." RADIOTHERAPY & ONCOLOGY, vol. 68, no. 3, September 2003 (2003-09), pages 305-313, XP002283036 ISSN: 0167-8140

   If not indicated otherwise, the relevant passages are those mentioned in the International Search Report.

3. The present application according to **claim 1** relates to a method for treating a proliferative disease comprising administering (a) an epothilone derivative of the given formula I, in combination with (b) ionizing radiation. **Claim 8** is directed to the use of a compound of formula I for the preparation of a medicament for use in combination with ionizing radiation for the delay of progression or treatment of a proliferative disease. Finally, **claim 11** is directed to a package comprising a compound of formula I, together with instructions for the use in combination with ionizing radiation for the treatment of a proliferative disease.

4. The present application does not meet the requirements of the PCT with respect to novelty (Art. 33(2)) for the following reasons.

Both **D1** and **D2** disclose the epothilone derivates of the present application, including epothilone B, and their use in the treatment of cancers, including glioma, colon carcinoma, etc. The documents also contemplate the combination of the compounds with radiotherapy. These documents are novelty destroying for present claims 1-11.

It should be noted that present claim 11 is regarded as directed to a pharmaceutical composition comprising the compound of formula I. The presence of written instructions with a pharmaceutical composition is not regarded as a distinguishing technical feature. Thus, claim 11 lacks novelty not only over **D1** and **D2**, but also over any document disclosing a pharmaceutical composition comprising said compound, irrespectively of the medical indication intended for it.

D3 discloses a method for enhancing the response of tumors to radiation exposure comprising the administration of an epothilone conjugate. **D3** does not specify the structure of the epothilone. However, it is considered that the person skilled in the art would certainly consider epothilone derivatives falling within the general formula I as compounds meant by **D3**. Thus, this document is also novelty destroying for the present application.

D4 was published after the priority date claimed in the present application and would be novelty destroying for the present application only if the priority turned out to be not valid. **D4** discloses that the epothilone B derivative BMS-247550 enhances the effect of radiation in solid tumors.

5. As far as the subject-matter of the claims is not rendered novel no inventive step can be recognised. Thus, the present application does also not meet the requirements of Art. 33(3) PCT.

However, it should be noted that any technical effect alleged in the application (for example a synergistic effect) has to be substantiated with technical data so that it can be considered for the assessment of inventive step.

6.1. For the assessment of the present claims 1-10 on the question whether they are

industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6.2. Claim 11 meets the criterion set forth in Article 33(4) PCT because their subject-matter is susceptible of industrial application.

Re Item VII

Certain defects in the international application

7. Claims 10 and 11 should be renumbered. Claim 9 is missing.